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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,488	01/15/2004	David G. Gorenstein	UTMB:1019	5963

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CHALKER FLORES, LLP
2711 LBJ FRWY
Suite 1036
DALLAS, TX 75234

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,488	GORENSTEIN ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-96* is/are pending in the application.

4a) Of the above claim(s) *18-36 and 38-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-17 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/21/04 & 5/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Transfer of application to art unit 1635

Note that due to applicant's election of invention this application has been reassigned to a new art unit and examiner.

Election/Restrictions

Applicant's election with traverse of group I, claims 1-17 and 37 and the further election of siRNAs, in the reply filed on December 21, 2005 is acknowledged. The traversal is on the ground(s) that groups I, VII and VIII have similar structure, effect and function and can be searched together. This is not found persuasive because invention I is directed to thioaptamers that mediate gene silencing while invention VIII is directed to a library of thioaptamers immobilized on beads, which would not be capable of mediating gene silencing. Invention VII also contains embodiments wherein the library is immobilized on beads and would similarly not mediate gene silencing. Thus, inventions I, VII and VIII do not have similar structures, effects and functions. Applicant also asserts that inventions II, III, V, VI, X and XI all have similar effect and function and may be examined together. This argument is not persuasive as the searches of these inventions with the elected invention would not be coextensive. Applicant states that the restriction requirement provides no substantive reason for restriction between groups I-IV, however the reasons for restriction between all inventions are set forth in the restriction requirement at pages 3-5. Applicant further states that inventions I-VII, X

and XI do not represent a serious burden on the examiner if not restricted but has provided no evidence to support this assertion. Applicant's arguments regarding the species election are moot since the non-elected species have been cancelled.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-36 and 38-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 21, 2005.

Objection to specification and requirement to comply with sequence rules

The specification is objected to because it fails to comply with 37 CFR 1.58(a), which states that the specification may not contain drawings. Figure 6 of the drawings has been reproduced within the specification on page 25 and must be deleted.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the following reason: Figures 2 and 6 contain sequences requiring SEQ ID NO but the identifier does not appear in either the figure or the brief description of the drawings.

To be considered responsive, any reply to this action must correct this deficiency, as this requirement will not be held in abeyance.

Priority

The parent applications do not provide support for thioaptamers, including siRNA, that mediate gene silencing, thus the priority date for this embodiment is January 15, 2004, the filing date of the instant application. If applicant believes that any of the prior applications provide support for this embodiment, it should be pointed out with particularity in the response to this action.

Information Disclosure Statement

The information disclosure statements submitted May 21 and May 24, 2004 have been considered. The Tuschl reference on the IDS of May 21 has been crossed out because the published applications database has no record of an application with this number.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites a thioaptamer comprising one or more α-thio modified nucleotide triphosphates. This claim is indefinite because is unknown whether the claim is meant

to recite that the nucleotide triphosphate is incorporated at one of the ends of the oligomer or if it is meant to refer to oligomers wherein the normal phosphodiester backbone is changed to be a triphosphate ester linkage.

Claim 37 recites a composition that mediates thioaptamer gene silencing. This claim is indefinite because it is unknown if thioaptamer gene silencing refers to a particular mechanism of gene silencing of if the claimed composition is meant to silence a thioaptamer.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claim 37 recites a pharmaceutical composition. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism.

The specification teaches the isolation of thioaptamers to VEE, the synthesis of a thioRNA library and the use of double stranded thioaptamers to inhibit the luciferase gene in cultured cells. The specification does not provide any examples where thioaptamers are used *in vivo* for any therapeutic purpose.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to use the claimed thioaptamers as pharmaceuticals. The specification provides an

example of inhibition of luciferase in HeLa cells, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results and the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene.

The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claim 37 is not enabled.

This rejection may be overcome by removing the word "pharmaceutical" from the preamble of this claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Baracchini (US 5,801,154).

The claimed invention is directed to isolated thioaptamers that mediate gene silencing. Thioaptamer is defined in the specification on page 6 as encompassing antisense oligonucleotides and ribozymes. The thioaptamer may comprise a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer may be fully or imperfectly complementary to the target gene and the silencing can occur through repression of translation, mRNA cleavage or binding to a 3'UTR. The thioaptamers can be 15-22 or 21-25 nucleotides in length and can comprise compositions with a carrier.

Baracchini et al. disclose antisense oligonucleotides that are targeted to and inhibit multi-drug resistance associated protein. These antisense oligonucleotides are 8-30 nucleotides in length, contain phosphorothioate linkages, are comprised of RNA or DNA, are targeted to numerous regions including the 3'UTR and are provided as compositions comprising a carrier (see claims 1 and 4-6 and columns 6-7). At column 3, lines 32-34 Baracchini et al. disclose that antisense oligonucleotides do not have to be 100% complementary to the target gene. It is known in the art that antisense inhibition occurs through an RNAse H mechanism that cleaves mRNA and prevents translation of the mRNA into protein.

Thus, Baracchini et al. disclose all limitations of and anticipate claims 1-4, 6, 8, 9, 15-17 and 37.

Claims 1-3, 6, 7, 9-12, 14-16 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell 2000).

The claimed invention is directed to thioaptamers that mediate gene silencing. The thioaptamer may comprise a 3' OH group and may be composed of ribonucleotides. The thioaptamer may comprise a double stranded RNA fully complementary to a target that silences the gene by mRNA cleavage and may be 15-22 or 21-25 nucleotides in length and can comprise compositions with a carrier. The thioaptamer may be part of a RISC complex, may be produced by a DICER complex and may be an siRNA.

Parrish et al. disclose double stranded RNAs comprising phosphorothioate linkages that are complementary to and inhibit the *unc-22* gene of *C. elegans* by RNA interference. As evidenced by the post-filing art of Zhang et al., Dicer is a multidomain ribonuclease that processes long dsRNAs to fragments of 21-25 nucleotides having 3'-OH termini during RNA interference and is part of the RISC complex. Although Parrish et al. are silent as to the cleavage of long dsRNAs into double stranded duplexes 21-25 nucleotides in length having 3'-OH termini, the long dsRNA molecules disclosed by Parrish et al. are necessarily cleaved into such duplexes. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property which is inherently present in the prior art does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art

reference. Inherent anticipation does not require recognition in the prior art. Since Parrish et al. teach phosphorothioate dsRNA and the resultant RNA interference, and it has since been discovered that this effect is mediated by the activity of Dicer, which cleaves long dsRNA into fragments that are 21-25 nucleotides long, the teachings of Parrish et al. anticipate the instant invention.

Thus, Parrish et al. disclose all limitations of and anticipate claims 1, 7, 10-12 and 14.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
March 8, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER